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In re Application of:	)	
	)	
Hsun-Lang Chang	)	Group Art Unit: 1614
	)	
Application No. 10/552,029	)	Examiner: To be assigned
	)	
Filing Date: October 18, 2006	)	Confirmation No. 6882
	)	
For: COMPOSITION AND METHOD FOR SUPPORTING CANCER TREATMENTS	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REQUEST FOR CORRECTED PATENT APPLICATION PUBLICATION UNDER 37 C.F.R. § 1.221(b)

The U.S. Patent and Trademark Office published the above-identified Application No. 10/552,029 as Publication No. US-2007-0166404-A1, on July 19, 2007. The published application contains mistakes that are the fault of the Office and may be material. Attached hereto are a copy of both the relevant page of the originally filed application and marked-up copy of the corresponding page of the published application containing the mistakes.

A mistake is material when it affects the public's ability to appreciate the technical disclosure of the patent application publication or determine the scope of the provisional rights that an applicant may seek to enforce upon issuance of a patent. See C.F.R.§1.221(b).

(A) On page 1 Abstract page, Inventor's name "Teuu" should read -- Tzuu"--

(see PCT cover page, para. (75) in the specifications as filed)

(B) On page 12, para. [0019], line 8, "-60 degree" should read --"-6 degree"--.

(see page 4, line 30, in the specifications as filed)

(C) On page 13, para. [0026], line 5, "62%" should read --"69%"--.

(see page 6, line 1, in the specifications as filed)

(D) On page 14, para [0030], line 8, "6" ± 10% should read --"60" ± 10%--

(see page 7, line 7, in the specification as filed)

(E) On page 15, para [0032], line 29, "803" ± 1.408 should read --"8.03" ± 1.408--

(on page 8, column 2 row 12 of the table in the specification as filed)

(F) On page 16, para [0034], line 7, "G-CSP" should read --G-CSF--

(on page 9, line 6, in the specification as filed)

(G) On page 16, para [0034], line 28, "6.21" ± 1.164 should read --"6.12" ± 1.164--

(on page 10, column 4 row 6 of the table in the specification as filed)

For at least the foregoing reasons, Applicants request that the Office correct the above-identified material mistake in the published application, which was the fault of the Office. Further, Applicants request that the Office forward a copy of the corrected published application or at least a notification of the occurrence or predicted occurrence of the corrected publication once it has been corrected.

Applicants believe that no Petition or fee is due in connection with this Request. However, if any Petition or fee is due, please grant the Petition and charge the fee

to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Date: August 28, 2007

By: 

Anna Y. Tsang
Reg. No. 48,003

Enclosures:
- Marked-up copy of the pages of the published application; and
- Corresponding pages of the original application

United States Patent Application 20070166404
Kind Code A1
Chang; Hsun-Lang ; et al. July 19, 2007

Composition and method for supporting cancer treatments

Abstract

The present invention relates to a novel composition comprising geranium oil and extracts from the roots of the plants of the genus Sophora, preferably Sophora tonkinesis. Said composition can be administered to mammalian animals undergoing cancer treatments, such as chemotherapy and radiation therapy, that would induce the side effect of bone marrow suppression. The administration can be made before, during and or after the cancer treatment.

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Claims

[0019] Certain specifications of geranium oil are set out in the National Standard of the People's Republic of China--GB 11959-89 which is incorporated herein by reference in their entirety, including any drawings. It adopts the same international standard of ISO 4731:1978 Oil of Geranium (Geranium Oil Standard). The Geranium Oil Standard specifies the outward characteristics of geranium oil, i.e. the geranium oil takes on a clear oil liquid form of a yellow greenish or amber color and has a distinct aroma. The same standard also specifies a relative density of 0.881-0.900 g/cm.sup.3, an optical rotation of -6-60.degree. to -14.degree., and a refractive index of 1.459-1.466 for geranium oil.

[0020] 2. Sophora tonkinesis

[0021] The root of Sophora tonkinesis takes on a long curved tublar form with branches and is typically about 0.3-1.5 centimeters in diameter. The root is hardened and difficult to break. Its surface color ranges from grayish brown to suntan brown with longitudinal wrinkles and holes. The root has a bean scent and is extremely bitter. It is grown mainly in parts of China, i.e. the Guangdong province, Guangxi province, Guizhou province, Yunan province, and Jiangxi province.

[0022] The root contains 0.93% of alkaloids, of which 0.52% is matrine and 0.35% is oxymatrine. The other alkaloids identified in the root of Sophora tonkinesis are anagyrine, methylcytisine, cytosine, sophocarpine, sophocarpine N-oxide, sophoramine, and sophoranol. The flavonic compounds identified in the root are sophoranone, sophoradin, sophoranochromene, sophoradochromene, pterocarpine, genistein, maackian, trifolirhizin, sitosterol, lu-peol, and a group of alkyl alcohol ester.

[0023] The principal alkaloid constituents of Sophora tonkinesis are also found in Sophora alopecuioides, Sophora moorcroftiana, and Euchresta strigillosa.

[0024] Result of pharmcokinetics study shows that in intravenous injections, the addition of geranium oil to matrine or oxymatrine will increase the absorption and metabolism of the respective compound (please see FIG. 2 and FIG. 3 for the changes in HPLC peak areas of matrine and matrine+geranium oil as time progresses). Furthermore, the composition of the present invention, containing oxymatrine, can also be taken orally to increase white blood cells. This is contrary to previously published data of animal experiments and clinical trials indicating that oxymatrine, when taken orally does not show any effect on increasing white blood cells, has to be injected through the muscles to increase white blood cells.

[0025] 3. Composition

[0026] The composition can be formed into powders (composition powders) through the following steps. First, geranium oil and the root of Sophora tonkinesis are prepared separately. .beta.-cyclodextrin is added to geranium oil to prevent evaporation, and excipients are added subsequently to form geranium oil powders. The geranium oil and the excipients are about 31% and 69%62% by weight, respectively, of the geranium oil powders. Next, the root of Sophora tonkinesis is cut into thin pieces and then grounded. About 250 grams of the grounded Sophora tonkinesis root is mixed with 3000 ml of water, about 12 times the weight of the grounded root. The mixture is then boiled in a steam distillation bottle to heat and reflux for about 1 hour. Afterwards; the scum on the surface of the liquid is removed, and the liquid is filtered through a 100 mesh screen. The filtered liquid is then concentrated and about 66 grams of solid extracts of Sophora tonkinesis is obtained. Excipients are added to the solid extractions to form Sophora tonkinesis root powders. The Sophora tonkinesis extractions and the excipients are about 60% and 40% by weight, respectively, of the Sophora tonkinesis powders. Subsequently, the geranium oil powders and the Sophora tonkinesis root powders are mixed together with additional excipients to form the composition of the present invention into powder forms, wherein the geranium oil powders, Sophora tonkinesis root powders, and the excipients are about 55.94%, 0.958%, and 43.102% by weight, respectively, of the composition powders. The weight ratio of geranium oil and extractions of Sophora tonkinesis within the composition are about 30:1. The excipients to be used in the process to form powders can be starch, sugar spheres, fructose, sorbital crystalline etc. and those commonly used by one skilled in the art.

[0027] Alternatively, the geranium oil powders and the Sophora tonkinesis root powders can be mixed with glycerine and gelatin to form capsules. The composition can also be made into dietary supplement, health food (functional food), and food additives. One can also decoct the Pelargonium plant and Sophora roots to obtain a liquid form of the composition for direct oral intake as a medicine soup or for making into syrup or other forms of liquid composition. Sophora roots the Pelargonium plant can also be taken orally, in an edible form, separately at a timed interval.

EXAMPLE

[0028] Composition powders were administered orally to immunologically normal mice that were also given the 5-Fluorouracil (5-Fu) drug intraperitoneally.

[0029] The test substance, i.e. the composition powders, was prepared by dissolving the content in PBS.

[0030] Animals tested are 12 male BALB/c mice of 6-7 weeks old, weighing 22.+-.2 grams, provided by Taiwan National University Medical Center Laboratory Animal Center. The animals are divided into two groups of 6 mice. Laboratory mice feeds manufactured by Purina (PMI5001) were used. Double-distilled water was provided for drinking. Laboratory mice wooden beddings manufactured by Beta Chip were used and changed 2-3 times weekly. Each group of 6 mice was kept in a feeding box of 29.2.times.19.times.12.7 (cm). Micro-Isolator.TM. VCL Rack Housing System 70084A was used. Temperature and humidity were kept at 23.+-.2.degree. C. and 606.+-.10% respectively. The mice were given twelve hours of light and twelve hours of darkness.

[0031] Doses of 21 mg and 7 mg of test substance dissolved in PBS were administered to the two groups of test animals respectively, in a feeding volume of 0.2 ml/mouse. The test substance were adnistered orally to the test animals the day after a single dose of the chemotherapeutic agent 5-Fu (135 mg/kg, IP) was given and then once daily for the next nine (10 doses total) and thirteen consecutive days (14 doses in total) for the first and second group of mice respectively. On day 10, the first group of mice was sacrificed by anesthetizing with CO2 and taking the blood from the heart to determine the cell counts of erythrocytes (RBC), platelets (PLT), total leukocytes (WBC), and differential leukocytes counts: lymphocytes (LY), monocytes (MO), and granulocytes (GR). On day 14, the second group of mice was sacrificed in the same manner to determine the same blood cell counts. The control employed in the experiment were normal mice without any injections.

[0032] As shown in the table below, 7 mg/mouse of test substance had the significant effect of increasing the number of red blood cells (RBC) and preventing the reduction of the number of WBC, LY, MO, and GR in mice injected with 5-Fu. The effect was more pronounced with the dosage of 7 mg/mouse. On day 10, the average WBC count of normal mice was 6.94.+-.1.647.times.10.sup.3/.mu.l, and the mice treated with 5-Fu had an average WBC count of 4.17.+-.0.677.times.10.sup.3/.mu.l. On the other hand, mice treated with 7 mg/mouse of test substance and 5-Fu had an average WBC count of 6.24.+-.1.924.times.10.sup.3/.mu.l, showing only 25% of the bone marrow suppression effect of 5-Fu. Differential leukocyte count showed that the suppression effect with respect to lymphocytes in test animals treated with 7 mg/mous of test substance and 5-Fu was only 12% of that of the test animals treated with 5-Fu only. With respect to monocytes, the suppression effect in test animals treated with 7 mg/mouse of test substance and 5-Fu was

only 21% of that of test animals treated with 5-Fu. With respect to granulocytes, the suppression effect in test animals treated with 7 mg/mouse of test substance and 5-Fu was 46% of that of test animals treated with 5-Fu. On day 14, the total leukocyte and differential leukocyte counts of mice treated with 7 mg/mouse of test substance and 5-Fu continued to increase to a higher level than that of mice treated with 5-Fu only. TABLE-US-00001 Effect of .sup..left brkt-top. geranium oil + Sophora tonkinesis extractions.right brkt-bot. on the side effects of reduction in blood cell counts caused by 5-Fu- 21 mg/mouse S. 7 mg/mouse S. Normal 5-Fu tonkinesis/5-Fu tonkinesis/5-Fu Day 10 RBC (10.sup.6/.mu.l) 9.09 .+-. 0.137 7.86 .+-. 0.171 7.66 .+-. 0.316 8.52 .+-. 0.627* PLT (10.sup.3/.mu.l) 990 .+-. 65.7 2828 .+-. 632.4 2441 .+-. 441.4 2099 .+-. 731.5 WBC (10.sup.3/.mu.l) 6.94 .+-. 1.647 4.17 .+-. 0.677 4.63 .+-. 0.772 6.24 .+-. 1.924* LY (10.sup.3/.mu.l) 5.30 .+-. 1.369 3.66 .+-. 0.648 4.15 .+-. 0.538 5.10 .+-. 1.261* MO (10.sup.3/.mu.l) 0.39 .+-. 0.035 0.25 .+-. 0.046 0.26 .+-. 0.154 0.36 .+-. 0.131* GR (10.sup.3/.mu.l) 1.24 .+-. 0.284 0.25 .+-. 0.050 0.22 .+-. 0.104 0.78 .+-. 0.559* Day 14 RBC (10.sup.6/.mu.l) 9.76 .+-. 0.269 8.09 .+-. 0.331 8.19 .+-. 0.160 8.23 .+-. 0.326 PLT (10.sup.3/.mu.l) 985 .+-. 216.5 2219 .+-. 750.2 2461 .+-. 195.4 2309 .+-. 687.5 WBC (10.sup.3/.mu.l) 8.03803 .+-. 1.408 7.98 .+-. 1.575 7.70 .+-. 0.599 8.48 .+-. 2.052 LY (10.sup.3/.mu.l) 6.53 .+-. 1.470 5.75 .+-. 0.880 6.10 .+-. 0.397 6.56 .+-. 1.591 MO (10.sup.3/.mu.l) 0.35 .+-. 0.092 0.59 .+-. 0.316 0.39 .+-. 0.124 0.44 .+-. 0.140 GR (10.sup.3/.mu.l) 1.15 .+-. 0.243 1.65 .+-. 0.756 1.21 .+-. 0.353 1.47 .+-. 0.560 1. Results are expressed in mean .+-. standard deviation (mean .+-. SD). 2. The experimental group and the 5-Fu group are compared using Dunnett's t-test, "*" means $p<0.05$, and "**" means $p<0.01$, and "***" means $p<0.001$.

[0033] The weight of mice treated with 7 mg/mouse and 21 mg/mouse decreased slightly, as the days progresses, as compared to the normal mice. TABLE-US-00002 Effect of geranium oil + Sophora tonkinesis extractions on the side effects of weight change caused by 5-Fu Day -2 Day 0 Day 6 Day 10 Day 14 Normal control 20.3 .+-. 1.90 21.6 .+-. 1.85 23.1 .+-. 1.94.sup.a 24.0 .+-. 1.89.sup.a 24.6 .+-. 2.21 (n = 18) (n = 18) (n = 18) (n = 12) (n = 6) 5-Fu 20.7 .+-. 0.90 22.0 .+-. 0.93 21.9 .+-. 1.20.sup.ab 22.3 .+-. 1.53.sup.b 23.5 .+-. 0.78 (n = 12) (n = 12) (n = 12) (n = 12) (n = 6) G-CSF/5-Fu 20.5 .+-. 1.76 22.0 .+-. 1.84 22.0 .+-. 1.84.sup.ab 22.5 .+-. 1.78.sup.ab 24.0 .+-. 1.64 (n = 12) (n = 12) (n = 12) (n = 12) (n = 6) 21 mg/mouse 19.6 .+-. 1.42 21.2 .+-. 1.38 21.4 .+-. 1.71.sup.b 21.4 .+-. 1.80.sup.b 22.3 .+-. 1.57 S. (n = 12) (n = 12) (n = 12) (n = 12) (n = 6) tonkinesis/5-Fu 7 mg/mouse 19.8 .+-. 1.50 21.4 .+-. 1.97 22.2 .+-. 1.67.sup.ab 22.6 .+-. 1.68.sup.ab 23.1 .+-. 3.04 S. (n = 12) (n = 12) (n = 12) (n = 12) (n = 6) tonkinesis/5-Fu 1. Results are expressed in mean .+-. standard deviation (mean .+-. SD). 2. At the same moment in time, Duncan's statistical analysis is used among the groups. Different alphabets stands for significant

differences ($p<0.05$).

[0034] In comparison with another type of treatment relating to the reduction of bone marrow suppression using G-CSF, the bone marrow suppression effect was not as significantly reduced as that ofthe tested novel composition ofthe present invention. On day 10, the normal mice's average WBC count was 6.94.+-.1.647.times.10.sup.3/.mu.l and the mice treated with 5-Fu had an average WBC count of 4.17.+-.0.677.times.10.sup.3 .mu.l. On the other hand, mice treated with 135 .mu.g/mouse of G-CSF~~G-CSF~~ and 5-Fu had an average WBC count of 5.46.+-.2.338.times.10.sup.3/.mu.l, showing 51% of the bone marrow suppression effect of 5-Fu. Differential leukocyte count showed that the suppression effect with respect to lymphocytes in test animals treated with 135 .mu.g/mouse of G-CSF and 5-Fu was only 18% of that of the test animals treated with 5-Fu only. With respect to monocytes, the suppression effect in test animals treated with 135 .mu.g/mouse of G-CSF and 5-Fu was only 7% of that of test animals treated with 5-Fu. With respect to granulocytes, the suppression effect in test animals treated with 135 .mu.g/mouse of G-CSF and 5-Fu was 54% of that of test animals treated with 5-Fu. On day 14, only the total leukocyte count and differential leukocyte count, with respect to lymphocytes of mice treated with 135 .mu.g/mouse of G-CSF and 5-Fu, continued to increase to a higher level than that of mice treated with 5-Fu only. TABLE-US-00003 Effect of G-CSF on the reduction of 5-Fu's side effect-change in blood cell counts 135 .mu.g/mouse Normal 5-Fu C-GSF/5-Fu Day 10 RBC (10.sup.6/.mu.l) 9.09 .+-. 0.137 7.86 .+-. 0.171 7.82 .+-. 0.424 PLT (10.sup.3/.mu.l) 990 .+-. 65.7 2828 .+-. 632.4 2303 .+-. 491.7 WBC (10.sup.3/.mu.l) 6.94 .+-. 1.647 4.17 .+-. 0.677 5.46 .+-. 2.338 LY (10.sup.3/.mu.l) 5.30 .+-. 1.369 3.66 .+-. 0.648 5.01 .+-. 1.372* MO (10.sup.3/.mu.l) 0.39 .+-. 0.035 0.25 .+-. 0.046 0.38 .+-. 0.141* GR (10.sup.3/.mu.l) 1.24 .+-. 0.284 0.25 .+-. 0.050 0.71 .+-. 0.268** Day 14 RBC (10.sup.6/.mu.l) 9.76 .+-. 0.269 8.09 .+-. 0.331 8.02 .+-. 0.340 PLT (10.sup.3/.mu.l) 985 .+-. 216.5 2219 .+-. 750.2 2105 .+-. 378.1 WBC (10.sup.3/.mu.l) 8.03 .+-. 1.408 7.98 .+-. 1.575 8.34 .+-. 1.454 LY (10.sup.3/.mu.l) 6.53 .+-. 1.470 5.75 .+-. 0.880 6.126~~.21~~ .+-. 1.164 MO (10.sup.3/.mu.l) 0.35 .+-. 0.092 0.59 .+-. 0.316 0.58 .+-. 0.266 GR (10.sup.3/.mu.l) 1.15 .+-. 0.243 1.65 .+-. 0.756 1.64 .+-. 0.405 1. Results are expressed in mean .+-. standard deviation (mean .+-. SD). 2. The experimental group and the 5-Fu group are compared using Dunnett's t-test, "*" means $p<0.05$, and "**" means $p<0.01$, and "***" means $p<0.001$.

[0035] The weight of the mice shows no significant difference among the groups. TABLE-US-00004 Effect of G-CSF on the reduction of 5-Fu's side effect-weight change Day -2 Day 0 Day 6 Day 10 Day 14 Normal control 20.3 .+-. 1.90 21.6 .+-. 1.85 23.1 .+-.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: COMPOSITION AND METHOD FOR SUPPORTING CANCER TREATMENTS

(57) Abstract: The present invention relates to a novel composition comprising geranium oil and extracts from the roots of the plants of the genus Sophora, preferably *Sophora tonkinesis*. Said composition can be administered to mammalian animals undergoing cancer treatments, such as chemotherapy and radiation therapy, that would induce the side effect of bone marrow suppression. The administration can be made before, during and or after the cancer treatment.

Fig. 2 shows the result of pharmcokinetics study of intravenous injection of matrine and matrine with and addition of geranium oil.

Fig. 3 shows the result of pharmcokinetics study of intravenous injection of oxymatrine and oxymatrine with the addition of geranium oil.

Detailed Description of the Invention

The present invention relates to a novel composition comprising geranium oil and extractions from the root of Sophora plants, preferably *Sophora tonkinesis*, and method of using the novel composition as a supporting drug or supplement in cancer treatments, preferably to reduce the bone marrow suppression side effect occurring in most of such treatments.

1. Geranium Oil

Geranium oil may be collected from steam distillation of the stem and leaves of the plant of division Magnoliophyta, class Magnoliopsida, order Geraniales, family Geraniaceae, and genus Pelargonium. Pelargoniums are native to South Africa and there are more than one hundred species in existence today, including hybridized garden species. Pelargoniums are now grown, and geranium oil is now produced, mainly in Algeria, Egypt, Morocco, Bourbon, China, and Australia. The present invention preferably uses geranium oil extracted from Pelargonium graveolens or Pelargonium roseum and Pelargonium terebinthinceum grown in Kunming City of the Yunan Province in China. A gas chromatography/mass spectroscopy (GC-MS) result of the geranium oil produced in Kunming shows the constituent compounds and their relative contents (see Fig. 1). The generally known main constituents of geranium oil are citronellol, geraniol, geranyl formate, citronellyl formate, linalool, trans-rose oxide, and cis-rose oxide.

Certain specifications of geranium oil are set out in the National Standard of the People's Republic of China - GB 11959-89 which is incorporated herein by reference in their entirety, including any drawings. It adopts the same international standard of ISO 4731:1978 Oil of Geranium (Geranium Oil Standard). The Geranium Oil Standard specifies the outward characteristics of geranium oil, i.e. the geranium oil takes on a clear oil liquid form of a yellow greenish or amber color and has a distinct aroma. The same standard also specifies a relative density of 0.881 – 0.900 g/cm^3, an optical rotation of -6°

the excipients are about 31% and 69% by weight, respetively, of the geranium oil powders. Next, the root of *Sophora tonkinesis* is cut into thin pieces and then grounded. About 250 grams of the grounded *Sophora tonkinesis* root is mixed with 3000 ml of water, about 12 times the weight of the grounded root. The mixture is then boiled in a steam distillation bottle to heat and reflux for about 1 hour. Afterwards, the scum on the surface of the liquid is removed, and the liquid is filtered through a 100 mesh screen. The filtered liquid is then concentrated and about 66 grams of solid extracts of *Sophora tonkinesis* is obtained. Excipients are added to the solid extractions to form *Sophora tonkinesis* root powders. The *Sophora tonkinesis* extractions and the excipients are about 60% and 40% by weight, respectively, of the *Sophora tonkinesis* powders. Subsequently, the geranium oil powders and the *Sophora tonkinesis* root powders are mixed together with additional excipients to form the composition of the present invention into powder forms, wherein the geranium oil powders, *Sophora tonkinesis* root powders, and the excipients are about 55.94%; 0.958%, and 43.102% by weight, respectively, of the composition powders. The weight ratio of geranium oil and extractions of *Sophora tonkinesis* within the composition are about 30:1. The excipients to be used in the process to form powders can be starch, sugar spheres, fructose, sorbital crystalline etc. and those commonly used by one skilled in the art.

Alternatively, the geranium oil powders and the *Sophora tonkinesis* root powders can be mixed with glycerine and gelatin to form capsules. The composition can also be made into dietary supplement, health food (functional food), and food additives. One can also decoct the Pelargonium plant and Sophora roots to obtain a liquid form of the composition for direct oral intake as a medicine soup or for making into syrup or other forms of liquid composition. Sophora roots the Pelargonium plant can also be taken orally, in an edible form, separately at a timed interval.

EXAMPLE

Composition powders were administered orally to immunologically normal mice that were also given the 5- Fluorouracil (5-Fu) drug intraperitoneally.

The test substance, i.e. the composition powders, was prepared by dissolving the content in PBS.

Animals tested are 12 male BALB/c mice of 6-7 weeks old, weighing 22±2 grams,

provided by Taiwan National University Medical Center Laboratory Animal Center. The animals are divided into two groups of 6 mice. Laboratory mice feeds manufactured by Purina (PMI5001) were used. Double-distilled water was provided for drinking. Laboratory mice wooden beddings manufactured by Beta Chip were used and changed 2-3 times weekly. Each group of 6 mice was kept in a feeding box of 29.2 x 19 x 12.7(cm). Micro-Isolator™ VCL Rack Housing System 70084A was used. Temperature and humidity were kept at 23±2°C and 60±10% respectively. The mice were given twelve hours of light and twelve hours of darkness.

Doses of 21mg and 7mg of test substance dissolved in PBS were administered to the two groups of test animals respectively, in a feeding volume of 0.2ml/mouse. The test substance were administered orally to the test animals the day after a single dose of the chemotherapeutic agent 5-Fu (135mg/kg, IP) was given and then once daily for the next nine (10 doses total) and thirteen consecutive days (14 doses in total) for the first and second group of mice respectively. On day 10, the first group of mice was sacrificed by anesthetizing with CO2 and taking the blood from the heart to determine the cell counts of erythrocytes (RBC), platelets (PLT), total leukocytes (WBC), and differential leukocytes counts: lymphocytes (LY), monocytes (MO), and granulocytes (GR). On day 14, the second group of mice was sacrificed in the same manner to determine the same blood cell counts. The control employed in the experiment were normal mice without any injections.

As shown in the table below, 7mg/mouse of test substance had the significant effect of increasing the number of red blood cells(RBC) and preventing the reduction of the number of WBC, LY, MO, and GR in mice injected with 5-Fu. The effect was more pronounced with the dosage of 7mg/mouse. On day 10, the average WBC count of normal mice was $6.94 \pm 1.647 \times 10^3/\mu l$, and the mice treated with 5-Fu had an average WBC count of $4.17 \pm 0.677 \times 10^3/\mu l$. On the other hand, mice treated with 7mg/mouse of test substance and 5-Fu had an average WBC count of $6.24 \pm 1.924 \times 10^3/\mu l$, showing only 25% of the bone marrow suppression effect of 5-Fu. Differential leukocyte count showed that the suppression effect with respect to lymphocytes in test animals treated with 7mg/mous of test substance and 5-Fu was only 12% of that of the test animals treated with 5-Fu only. With respect to monocytes, the suppression effect in test animals treated with 7mg/mouse of test

substance and 5-Fu was only 21 % of that of test animals treated with 5-Fu. With respect to granulocytes, the suppression effect in test animals treated with 7mg/mouse of test substance and 5-Fu was 46% of that of test animals treated with 5-Fu. On day 14, the total leukocyte and differential leukocyte counts of mice treated with 7mg/mouse of test substance and 5-Fu continued to increase to a higher level than that of mice treated with 5-Fu only.

Effect of 「geranium oil + *Sophora tonkinesis* extractions」 on the side effects of reduction in blood cell counts caused by 5-Fu –

	Normal	5-Fu	21 mg/mouse S. tonkinesis /5-Fu	7 mg/mouse S. tonkinesis /5-Fu
Day 10				
RBC (10^6/μl)	9.09 ± 0.137	7.86 ± 0.171	7.66 ± 0.316	8.52 ± 0.627*
PLT (10^3/μl)	990 ± 65.7	2828 ± 632.4	2441 ± 441.4	2099 ± 731.5
WBC (10^3/μl)	6.94 ± 1.647	4.17 ± 0.677	4.63 ± 0.772	6.24 ± 1.924*
LY (10^3/μl)	5.30 ± 1.369	3.66 ± 0.648	4.15 ± 0.538	5.10 ± 1.261*
MO (10^3/μl)	0.39 ± 0.035	0.25 ± 0.046	0.26 ± 0.154	0.36 ± 0.131*
GR (10^3/μl)	1.24 ± 0.284	0.25 ± 0.050	0.22 ± 0.104	0.78 ± 0.559*
Day 14				
RBC (10^6/μl)	9.76 ± 0.269	8.09 ± 0.331	8.19 ± 0.160	8.23 ± 0.326
PLT (10^3/μl)	985 ± 216.5	2219 ± 750.2	2461 ± 195.4	2309 ± 687.5
WBC (10^3/μl)	8.03 ± 1.408	7.98 ± 1.575	7.70 ± 0.599	8.48 ± 2.052
LY (10^3/μl)	6.53 ± 1.470	5.75 ± 0.880	6.10 ± 0.397	6.56 ± 1.591
MO (10^3/μl)	0.35 ± 0.092	0.59 ± 0.316	0.39 ± 0.124	0.44 ± 0.140
GR (10^3/μl)	1.15 ± 0.243	1.65 ± 0.756	1.21 ± 0.353	1.47 ± 0.560

1. Results are expressed in mean ±standard deviation (mean ± SD).
2. The experimental group and the 5-Fu group are compared using Dunnett's t-test, "*" means $p<0.05$, "**" means $p<0.01$, and "****" means $p<0.001$.

The weight of mice treated with 7mg/mouse and 21mg/mouse decreased slightly, as the days progresses, as compared to the normal mice.

Effect of「geranium oil + *Sophora tonkinesis* extractions」on the side effects of weight change caused by 5-Fu

	Day -2	Day 0	Day 6	Day 10	Day 14
Normal control	20.3 ± 1.90 (n=18)	21.6 ± 1.85 (n=18)	23.1 ± 1.94[a] (n=18)	24.0 ± 1.89[a] (n=12)	24.6 ± 2.21 (n=6)
5-Fu	20.7 ± 0.90 (n=12)	22.0 ± 0.93 (n=12)	21.9 ± 1.20[ab] (n=12)	22.3 ± 1.53[b] (n=12)	23.5 ± 0.78 (n=6)
G-CSF/5-Fu	20.5 ± 1.76 (n=12)	22.0 ± 1.84 (n=12)	22.0 ± 1.84[ab] (n=12)	22.5 ± 1.78[ab] (n=12)	24.0 ± 1.64 (n=6)

21 mg/mouse *S. tonkinesis*/5-Fu	19.6 ± 1.42 (n=12)	21.2 ± 1.38 (n=12)	21.4 ± 1.71 [b] (n=12)	21.4 ± 1.80 [b] (n=12)	22.3 ± 1.57 (n=6)
7 mg/mouse *S. tonkinesis*/5-Fu	19.8 ± 1.50 (n=12)	21.4 ± 1.97 (n=12)	22.2 ± 1.67 [ab] (n=12)	22.6 ± 1.68 [ab] (n=12)	23.1 ± 3.04 (n=6)

1. Results are expressed in mean ±standard deviation (mean ± SD).
2. At the same moment in time, Duncan's statistical analysis is used among the groups. Different alphabets stands for significant differences ($p<0.05$).

In comparison with another type of treatment relating to the reduction of bone marrow suppression using G-CSF , the bone marrow suppression effect was not as significantly reduced as that of the tested novel composition of the present invention. On day 10, the normal mice's average WBC count was 6.94 ± 1.647× 10^3/µl, and the mice treated with 5-Fu had an average WBC count of 4.17 ± 0.677 ×10^3/µl. On the other hand, mice treated with 135µg/mouse of G-CSF and 5-Fu had an average WBC count of 5.46 ± 2.338×10^3/µl, showing 51% of the bone marrow suppression effect of 5-Fu. Differential leukocyte count showed that the suppression effect with respect to lymphocytes in test animals treated with 135µg /mouse of G-CSF and 5-Fu was only 18% of that of the test animals treated with 5-Fu only. With respect to monocytes, the suppression effect in test animals treated with 135µg /mouse of G-CSF and 5-Fu was only 7 % of that of test animals treated with 5-Fu. With respect to granulocytes, the suppression effect in test animals treated with 135µg /mouse of G-CSF and 5-Fu was 54% of that of test animals treated with 5-Fu. On day 14, only the total leukocyte count and differential leukocyte count, with respect to lymphocytes of mice treated with 135µg /mouse of G-CSF and 5-Fu, continued to increase to a higher level than that of mice treated with 5-Fu only.

Effect of G-CSF on the reduction of 5-Fu's side effect- change in blood cell counts

	Normal	5-Fu	135 µg/mouse C-GSF/5-Fu
Day 10			
RBC (10^6/µl)	9.09 ± 0.137	7.86 ± 0.171	7.82 ± 0.424
PLT (10^3/µl)	990 ± 65.7	2828 ± 632.4	2303 ± 491.7
WBC (10^3/µl)	6.94 ± 1.647	4.17 ± 0.677	5.46 ± 2.338
LY (10^3/µl)	5.30 ± 1.369	3.66 ± 0.648	5.01 ± 1.372*
MO (10^3/µl)	0.39 ± 0.035	0.25 ± 0.046	0.38 ± 0.141*

GR (10^3/μl)	1.24 ± 0.284	0.25 ± 0.050	0.71 ± 0.268**
Day 14			
RBC (10^6/μl)	9.76 ± 0.269	8.09 ± 0.331	8.02 ± 0.340
PLT (10^3/μl)	985 ± 216.5	2219 ± 750.2	2105 ± 378.1
WBC (10^3/μl)	8.03 ± 1.408	7.98 ± 1.575	8.34 ± 1.454
LY (10^3/μl)	6.53 ± 1.470	5.75 ± 0.880	6.12 ± 1.164
MO (10^3/μl)	0.35 ± 0.092	0.59 ± 0.316	0.58 ± 0.266
GR (10^3/μl)	1.15 ± 0.243	1.65 ± 0.756	1.64 ± 0.405

1. Results are expressed in mean ±standard deviation (mean ± SD).
2. The experimental group and the 5-Fu group are compared using Dunnett's t-test, "*" means $p<0.05$, "**" means $p<0.01$, and "****" means $p<0.001$.

The weight of the mice shows no significant difference among the groups.

Effect of G-CSF on the reduction of 5-Fu's side effect- weight change

	Day -2	Day 0	Day 6	Day 10	Day 14
Normal control	20.3 ± 1.90 (n=18)	21.6 ± 1.85 (n=18)	23.1 ± 1.94 (n=18)	24.0 ± 1.89[a] (n=12)	24.6 ± 2.21 (n=6)
5-Fu	20.7 ± 0.90 (n=12)	22.0 ± 0.93 (n=12)	21.9 ± 1.20 (n=12)	22.3 ± 1.53[b] (n=12)	23.5 ± 0.78 (n=6)
G-CSF/5-Fu	20.5 ± 1.76 (n=12)	22.0 ± 1.84 (n=12)	22.0 ± 1.84 (n=12)	22.5 ± 1.78[b] (n=12)	24.0 ± 1.64 (n=6)

1. Results are expressed in mean ±standard deviation (mean ± SD).
2. At the same moment in time, Duncan's statistical analysis is used among the groups. Different alphabets stands for significant differences ($p<0.05$).

The composition of *Sophora tonkinesis* and geranium oil does in fact significantly reduces the bone marrow suppression effect of 5-Fu and is performing better even than the G-CSF treatment. The ability of the composition of the present invention to reduce bone marrow suppression effect makes it a good candidate as a supporting drug or supplement to be used in cancer treatments that induce bone marrow suppression. In particular, the composition of the present invention may be used with chemotherapy and or radiation therapy to increase the leukocyte count. For example, the composition of the present invention may be used with 5-Fu, doxorubincin and other chemotherapeutic agents just as Neupogen is also used with 5-Fu as well as doxorubincin and many other types of chemotherapy to stimulate the growth of neutrophils whose number is originally reduced by chemotherapy.